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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	#22

DATE MAILED: 04/28/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/397,225	Applicant(s) Perricaudet et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Mar 23, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 6, and 9-39* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3, 6, 9, 10, and 12-39* is/are rejected.

☒ Claim(s) *2 and 11* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *19*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

The amendment filed 3/23/98 has been received. The finality of the previous Office action is withdrawn and prosecution is re-opened in view of the new grounds of rejection set forth below. Consequently, the amendment to claims 36 and 37 has been entered. The amendment to claim 39 has not been entered because the word "regulatable" was not present in the original claim 39 (added by amendment 10/10/97, and was not underlined in the amendment filed 3/23/98).

Priority

Receipt is acknowledged of FR 93/08596 and FR 94/04590 submitted under 35 U.S.C. 119(a)-(d), which have been placed of record in the file. However, applicant cannot rely upon the foreign priority papers to overcome a rejection made under 35 USC 102/103 because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Objections

Claims 2, 3, 6, 9-30, 32, 33 and 37-39 are objected to because of the following informalities: In claims 2, 3, 6, 9-18, 32 and 37-39, "An adenovirus according to claim" should be --The defective recombinant adenovirus according to claim--. In claims 20-27 and 33, "A cell line" should be --The cell line--. In claims 19 and 28, "a defective recombinant adenovirus" should be --the defective recombinant adenovirus--. In claim 29, "a recombinant adenovirus" should be --the defective recombinant adenovirus--. In claim 30, "A composition" should be --The composition--. In claim 13, the members of the Markush group should be singular, not plural. In claim 39, "gene modification(s)" should be replaced with --one or more genetic modifications--. Appropriate correction is required.

Information Disclosure Statement

With respect to the US patent applications listed on the PTO-1449, 08/417,674 and 08/111,947 have no relevance whatsoever with the claimed invention, and Perricaudet et al. is not the inventive entity of these applications. With respect to 08/553,317, it has been considered; however, application numbers should not be listed on a PTO-1449. A PTO-1449 should list only publications or papers that are available to the public, patent applications are confidential and not freely available to the public. Also, the references listed on a PTO-1449 would appear on the cover of a patent. In the future, related applications should be disclosed in an information disclosure statement, but not listed on a PTO-1449 that may accompany the statement. WO

94/26914 and WO 94/28152 have been considered only to the extent of the English abstract, since no translation of the remainder of these documents was provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 26 and 33 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Claims to cell lines comprising E2 or E4 genes without recitation that the genes are under control of inducible promoters, which are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). As stated in the specification at page 20, lines 25-27, the E2 and E4 genes are placed under control of inducible promoters because the gene products are cytotoxic.

Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no support in the specification as originally filed for the limitation that an adenovirus comprise part of either the E2 or E4 region, or in the case of claim

34, that no other adenoviral genes are present. Examples 3 and 4 show adenovirus comprising the E2 region or the E4 region, each of which comprises several genes. The specification simply does not mention an adenovirus that retains only the ITRs, packaging sequence and "part" of either the E2 or E4 region. A "part" need not comprise even one intact gene from either of these regions. With respect to the limitation in claim 34 that no other adenoviral genes are present appears no where in the specification, the DNA present in the adenovirus described in the specification clearly comprises genes transcribed from the antisense strand of the cloned E2 region. (see Fig. 1 of Berkner (1988) BioTechniques 6(7): 616).

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The claim appears to recite that the adenoviral genome comprises all or part of the E2 region but no other adenoviral genes other than E2 genes. As is well known in the art, and shown in Berkner (1988) BioTechniques 6(7): 616 (page 618, Fig. 1), the adenoviral genome is highly compressed with numerous overlapping gene regions transcribed in the same and opposite directions. The E2 region of adenovirus completely overlaps a large number of other adenoviral genes such as the L1-L4 genes, the VA gene and the IVa2 gene, most of which are transcribed from the antisense strand of the E2 genes. The specification provides no working examples of such an adenovirus and absolutely no guidance on how to include E2 genes without including any

other adenoviral genes whose transcription units overlap that of the E2 genes, if indeed it is even possible to do so. Clearly, any such endeavor would require undue experimentation in the face of a total lack of guidance and the knowledge in the prior art which suggests that it such adenovirus are a physical impossibility.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-27 and 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites "tumor suppressor genes", which are not gene products.

Claim 14 is indefinite for recitation of "DNA encodes an antisense sequence"; the meaning of "encodes" in this context is unclear. A nucleotide sequence can "encode" a polypeptide. Any heterologous gene that comprises a polypeptide coding sequence comprises both sense and "antisense" sequences, so it is unclear whether the recited limitation further limits claim 1.

Claim 15 recites "capable of generating" with reference to an immune response. The use of "capable of" implies a latent property and the conditions under which the property is manifested are unclear and not defined in the claim. The phrase should be replaced with --which

produces--, and the claim should also recite under what conditions the response is produced to the antigenic peptide, such as when introduced into a mammal.

Claim 16 recites "antigenic peptide specific for a virus"; "specific" in this context is vague and unclear. In what way is the antigenic peptide "specific" for a virus?

Claim 17 recites that the heterologous DNA sequence further comprises a promoter, and claim 18 recites that the heterologous DNA sequence further comprises a signal sequence. However, it is unclear if the "promoter" and "signal sequence" have any relationship with the genes present in the heterologous DNA sequence, other than proximity. In the case of a promoter, if the promoter is operationally linked to the gene, then claim 17 would not further limit claim 12, since a gene is understood in the art to comprise a promoter and often also comprises transcriptional regulatory elements.

Claim 19 recites the limitation "the genes" in line 3. There is insufficient antecedent basis for this limitation in the claim. "the" should be replaced with --adenoviral--. This also renders the claims dependent on claim 19 indefinite.

Claim 27 is indefinite for recitation of "obtained from the line 293". Recitation of "the line 293" lacks antecedent basis in the claim, and it is unclear what "obtained from" and "the line 293" mean. The phrase should be replaced with --made from human embryonic kidney cell line 293--.

Claims 34-35 are indefinite for recitation of "adenovirus consisting essentially of" and "the ... region or part thereof is the sole adenoviral gene". An adenovirus must consist of more than DNA to be an adenovirus, consequently "consisting essentially of" makes no sense in this context.

Also, the legal definition of "consisting essentially of" was set forth in *Ex parte* Davis and Tuukkanen 80 USPQ 448 (Patent Office Board of Appeals) 1949 and applies to compositions, such as an adenovirus, but not compounds, such as DNA. Consequently, this part of the rejection cannot be overcome by stipulating that the genome of the adenovirus "consists essentially of" something. The phrase "the sole adenoviral gene" lacks antecedent basis in the claims. Also, neither the E2 region nor E4 region is equivalent to a "gene", but comprise several genes. Also, even "part thereof" would not necessarily be a single gene, but could simply be part of a gene. Furthermore, in the case of the E2 region, it is unclear how the E2 genes could be the only adenoviral genes present since the E2 region is inextricably linked to other adenoviral genes, such as the IVa2, VA and L1-L4, which are transcribed from the same sense or antisense strand as the E2 genes. See Berkner, 1988 (Ref. C1), page 618, Fig. 1.

Claim 36 recites the limitations "the E4 genes" and in line 5 and "the coding region" in line 6. There is insufficient antecedent basis for these limitations in the claim. This renders claims 37-39 indefinite as well.

Claim 39 is vague and unclear since because the phrase "whereby production of said genes is according to a desired mode of regulation" is ambiguous since the beginning of the claim recites that E4 genes are nonfunctional. Further, the phrase "production of said genes" makes no sense; in what way are the genes produced. Applicant's arguments filed 3/23/98 have been fully considered but they are not persuasive. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In*

re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "non-functional" is used by the claim to include regulation of expression by some "desired mode of regulation" while the accepted meaning is inactive, i.e. no expression whatsoever. While one can say that replacing the endogenous promoter with a heterologous promoter might result in altered gene function, it certainly would not render the gene "non-functional" as that term would be understood in the art. The replacement of "according to a desired mode of regulation" with "regulatable" would not correct the problem, especially since the E4 genes are normally "regulatable" by the level of E1 gene expression.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Gregory et al., US 5,670,488.

Gregory et al. disclose two types of defective recombinant human group C adenoviruses comprising adenoviral ITR sequences, the packaging or encapsulation sequence psi, a heterologous gene, and deletions of various adenoviral early genes, and compositions comprising

these adenoviruses in a pharmaceutically acceptable carrier, which anticipate the claims. The first type are the pseudoadenoviral vectors, PAVs, in which the only adenoviral sequences present are the ITRs and psi and optionally adenoviral promoters, i.e. all adenoviral coding sequences and most non-coding sequences have been deleted. The second type have deletions in the E4 region rendering all E4 genes non-functional except either ORF3 or ORF6, preferably ORF6, and optionally deletions of the E1 region or E3 region or both. The reference discloses human embryo kidney 293 cells which complement the E1 deletion of the second type of adenovirus and presumably comprise the human glucocorticoid receptor gene. The heterologous DNA disclosed for either type of vector comprise a promoter operatively linked to a therapeutic polypeptide coding sequence. The polypeptide coding sequence can include the a sequence encoding a signal sequence, e.g. the CFTR coding sequence. The heterologous DNA can comprise therapeutic genes encoding Factors VIII and IX, CFTR, alpha-1-antitrypsin, superoxide dismutase, interferons, and DNases . Although the compositions were administered intranasally, the compositions were buffer suspensions and therefore acceptable for injection. (See Fig. 16A; col. 3, line 60 to col. 4, line 41; col. 12, line 1 to col. 13, line 45; col. 27, lines 40-56; col. 37, line 52 to col. 38, line 13; col. 101-104, claims 1-19.)

The first type of adenovirus, the PAVs, anticipate all of the claims, while the second type anticipates claims 1, 3, 9, 12-14, 17, 18, 28, 30, and 31. For this second type of adenovirus, claims 1 and 31 recite that "E4 genes have been rendered non-functional by deletion". This phrase embraces adenovirus in which at least two of the E4 ORFs have been rendered non-functional,

and is not limited to adenoviruses where all E4 genes are non-functional. With respect to claim 14, since the meaning of "encodes" is unclear, it has been interpreted as --comprises--, and any heterologous gene that comprises a polypeptide coding sequence comprises both sense and "antisense" sequences of the coding sequence. In the case of claims 36-37, the claim embraces PAV adenovirus in which the non-coding regions have been deleted in addition to the coding regions.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 9, 12, 14-17, 19, 23, 27, 28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., US 4,920,209 in view of Gregory et al., US 5,670,488.

Davis et al. discloses defective recombinant human type C adenovirus with deletions in E3 and E1 comprising heterologous DNA encoding antigenic/immunogenic peptides of viruses such as hepatitis B virus and HIV under control of a promoter (col. 2, line 49 to col. 4, line 17). With respect to claim 14, since the meaning of "encodes" is unclear, it has been interpreted as --comprises--, and any heterologous gene that comprises a polypeptide coding sequence comprises both sense and "antisense" sequences of the coding sequence. The reference does not disclose adenovirus wherein "E4 genes have been rendered non-functional by deletion".

However, Gregory et al. discloses adenovirus comprising a gene of interest in which some of the adenoviral E4 genes have been rendered non-functional by deletion, in addition to deletion of E1 and/or E3 genes, which allows for accommodation of larger inserts of heterologous DNA. The reference also discloses the human embryo kidney cell line for propagating the virus, which presumably has the human glucocorticoid receptor gene (col. 12, line 52 to col. 13, line 11; claims 1-6).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made the adenovirus of Davis et al. with a deletion in E4 as taught by Gregory et al. with a reasonable expectation of success for the purpose of accommodating larger inserts. For example, with the increased cloning capacity afforded by the E4 deletion, one skilled in the art would recognize that multiple peptide coding sequences for different antigenic peptides could be inserted.

Allowable Subject Matter

Claims 2 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 20-22, 24-26 and 33 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112 set forth in this Office action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, Ph.D., can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe, Ph.D. April 24, 1998
Patent Examiner
Art Unit 1632